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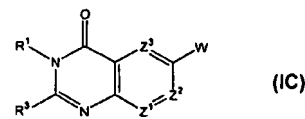
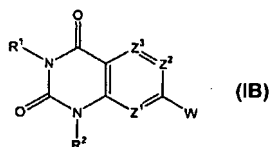
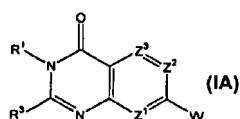
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- with amended claims

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: GUANIDINO-SUBSTITUTED QUINAZOLINONE COMPOUNDS AS MC4-R AGONISTS



(57) Abstract: A variety of small molecule, guanidine-containing molecules capable of acting as MC4-R agonists are provided. The compounds are useful in treating MC4-R mediated diseases when administered to subjects. The compounds have the structure IA, IB, and IC where the values of the variables are defined herein.

AMENDED CLAIMS

[received by the International Bureau on 15 December 2004 (15.12.04);
original claims 1, 8, 10 amended; new claims 29-92 added; remaining claims unchanged (22 pages)]

35 $R^{4'}$ is selected from H, or substituted or unsubstituted alkyl,
36 alkenyl, alkynyl, cycloalkyl, heterocyclalkyl, cycloalkylalkyl, aryl, heteroaryl,
37 heterocycl, arylalkyl, or heteroarylalkyl groups; and
38 pharmaceutically acceptable salts thereof, stereoisomers
39 thereof, tautomers thereof, hydrates thereof, or solvates thereof.

1 2. The compound of claim 1, wherein one of $R^{1'}$ or $R^{2'}$ is a
2 substituted or unsubstituted pyrrolidinylalkyl group.

1 3. The compound of claim 2, wherein one of $R^{1'}$ or $R^{2'}$ is a
2 substituted or unsubstituted pyrrolidinylmethyl group or is a substituted or
3 unsubstituted pyrrolidineethyl group.

1 4. The compound of claim 1, wherein R^3 is H.

1 5. The compound of claim 1, wherein Z^1 is a CR^4 group, Z^2
2 is a CR^5 group, and Z^3 is a CR^6 group.

1 6. The compound of claim 1, wherein $R^{3'}$ is selected from
2 substituted or unsubstituted cycloalkyl, polycyclic cycloalkyl, alkenyl, alkyl, or
3 aryl groups.

1 7. The compound of claim 1, wherein R^1 is a 2,4-
2 disubstituted phenylethyl group.

1 8. The compound of claim 1, wherein R^1 is selected from a
2 phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-
3 phenoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-
4 chlorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl, 2-
5 methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-
6 methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolyethyl, 4-
7 hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-
8 fluoro-4-methylphenylethyl, 2-fluoro-4-chlorophenylethyl, 2-fluoro-4-

29 heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclalkyl, or alkylthioalkyl
30 groups;

31 $R^{3'}$ is selected from H, or substituted or unsubstituted aryl, alkyl,
32 alkenyl, alkynyl, cycloalkyl, heteroaryl, heterocyclyl, heterocyclalkyl, arylalkyl,
33 heteroarylalkyl, or cycloalkylalkyl groups;

34 $R^{4'}$ is selected from H, or substituted or unsubstituted alkyl,
35 alkenyl, alkynyl, cycloalkyl, heterocyclalkyl, cycloalkylalkyl, aryl, heteroaryl,
36 heterocyclyl, arylalkyl, or heteroarylalkyl groups; and

37 pharmaceutically acceptable salts thereof, stereoisomers
38 thereof, tautomers thereof, hydrates thereof, or solvates thereof.

1 11. The compound of claim 10, wherein the heterocyclic ring
2 formed by $R^{1'}$ and $R^{2'}$ and the nitrogen to which they are bound is a
3 substituted piperazine.

1 12. The compound of claim 11, wherein the piperazine is
2 substituted with a group selected from a phenylalkyl group, a substituted or
3 unsubstituted phenyl group, an $-alkyl-SCH_3$ group, an indolylalkyl group, a
4 morpholinylalkyl group, a pyridyl group, a piperidinyl group, or a
5 tetrahydrofuranylalkyl group.

1 13. The compound of claim 10, wherein the heterocyclic ring
2 formed by $R^{1'}$ and $R^{2'}$ and the nitrogen to which they are bound is a
3 substituted piperidine.

1 14. The compound of claim 13, wherein the piperidine is
2 substituted with a group selected from a phenylalkyl group, a substituted or
3 unsubstituted phenyl group, an $-alkyl-SCH_3$ group, an indolylalkyl group, a
4 morpholinylalkyl group, a pyridyl group, a piperidinyl group, or a
5 tetrahydrofuranylalkyl group.

1 23. A method of treating an MC4-R mediated disease,
2 comprising administering to a subject in need thereof, the compound
3 according to any one of claims 10-19.

1 24. The method according to claim 23, wherein the disease is
2 obesity or type II diabetes.

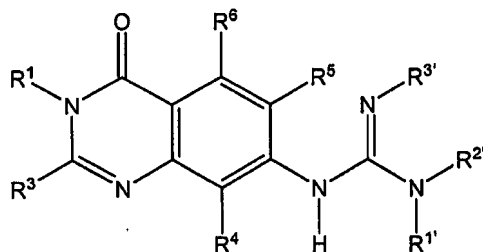
1 25. Use of a compound of any one of claims 1-8 in the
2 preparation of a medicament for treating an MC4-R mediated disease.

1 26. The use of claim 25, wherein the MC4-R mediated
2 disease is obesity or type II diabetes.

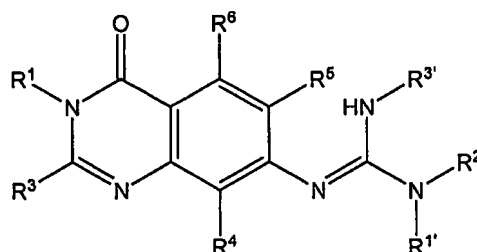
1 27. Use of a compound of any one of claims 10-19 in the
2 preparation of a medicament for treating an MC4-R mediated disease.

28. The use of claim 27, wherein the MC4-R mediated
disease is obesity or type II diabetes.

1 29. A compound of formula VA, VB, mixtures thereof, or
2 pharmaceutically acceptable salts of the compound,



VA



VB

3
4 wherein

5 R¹ is selected from substituted or unsubstituted arylalkyl,
6 heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclalkyl,
7 cycloalkylalkyl, alkenyl, alkynyl, or alkyl groups;

8 R^3 is selected from substituted or unsubstituted aryl, heteroaryl,
9 heterocyclyl, cycloalkyl, heterocyclylalkyl, or cycloalkylamino groups;

10 R^4 , R^5 , and R^6 are independently selected from H, Cl, I, F, Br,
11 OH, NH_2 , CN, NO_2 , or substituted or unsubstituted alkoxy or alkyl groups;

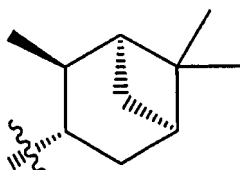
12 $R^{1'}$ and $R^{2'}$, together with the nitrogen to which they are bound,
13 form a substituted or unsubstituted heterocyclyl group; and

14 $R^{3'}$ is selected from substituted or unsubstituted cycloalkyl
15 groups.

1 30. The compound of claim 29, wherein R^4 , R^5 , and R^6 are all
2 H.

1 31. The compound of claim 29, wherein $R^{3'}$ is a substituted
2 or unsubstituted polycyclic cycloalkyl group.

1 32. The compound of claim 31, wherein $R^{3'}$ is a substituted
2 or unsubstituted polycyclic cycloalkyl group of formula VIII



VIII

3
1 33. The compound of claim 29, wherein R^1 is a substituted or
2 unsubstituted arylalkyl group.

1 34. The compound of claim 33, wherein R^1 is a substituted
2 phenylethyl group.

1 35. The compound of claim 34, wherein R^1 is a 4-substituted
2 phenylethyl group or is a 2,4-disubstituted phenylethyl group.

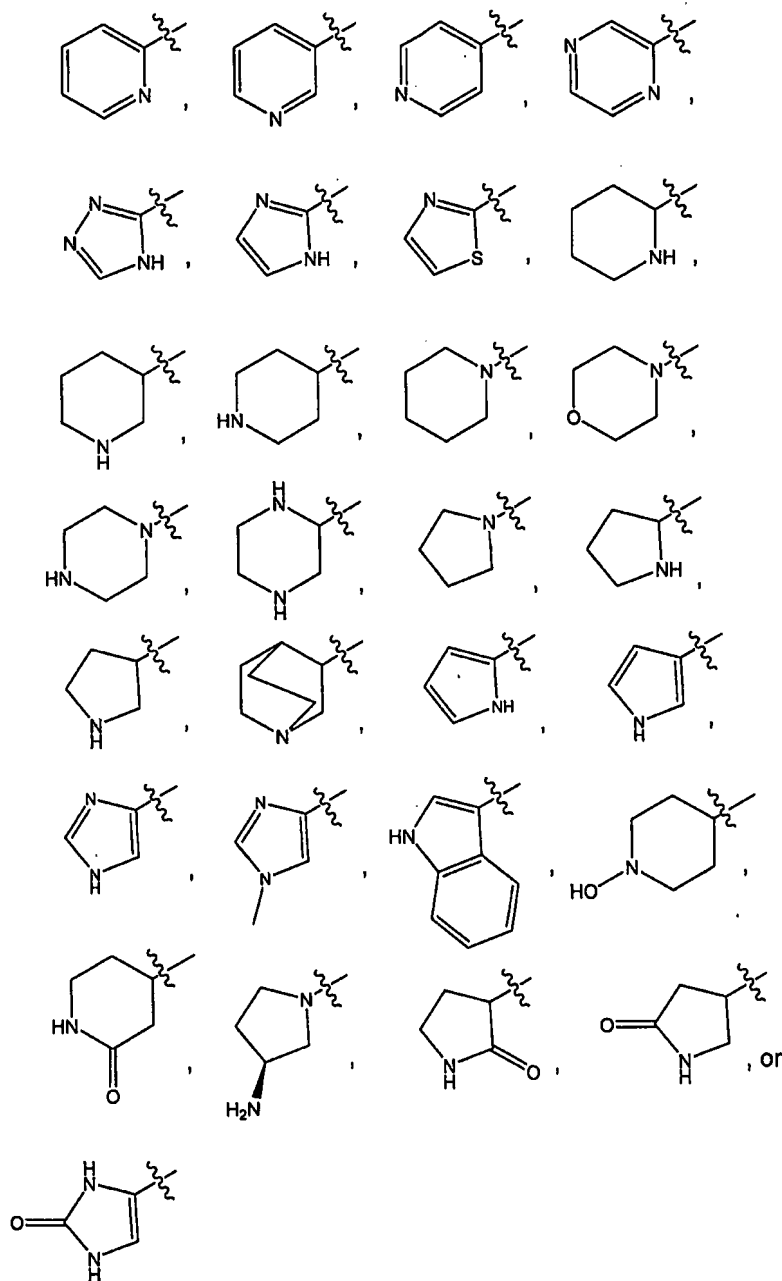
1 36. The compound of claim 34, wherein R^1 is selected from
2 2-fluoro-4-methoxyphenylethyl, 2-chloro-4-methoxyphenylethyl, 4-
3 fluorophenylethyl, 4-chlorophenylethyl, 4-chloro-2-fluorophenylethyl, 2,4-
4 dichlorophenylethyl, 4-bromophenylethyl, or 4-bromo-2-fluorophenylethyl
5 groups.

1 37. The compound of claim 29, wherein R^1 is selected from
2 phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-
3 phenoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-
4 chlorophenylethyl, 4-fluorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl,
5 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-
6 methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolyethyl, 4-
7 hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-
8 fluoro-4-methylphenylethyl, 4-chloro-2-fluorophenylethyl, 4-bromo-2-
9 fluorophenylethyl, 2-fluoro-4-methoxyphenylethyl, 2-trifluoromethyl-4-
10 fluorophenylethyl, 2,4-difluorophenylethyl, 2,4-dimethylphenylethyl, 2,4-
11 dimethoxyphenylethyl, (2-pyridyl)ethyl, (3-pyridyl)ethyl, (4-pyridyl)ethyl,
12 (pyridyl)(hydroxymethyl)ethyl, or (phenyl)(hydroxymethyl)ethyl groups.

1 38. The compound of claim 29, wherein R^3 is selected from
2 substituted or unsubstituted heterocyclyl groups, or substituted or
3 unsubstituted heteroaryl groups.

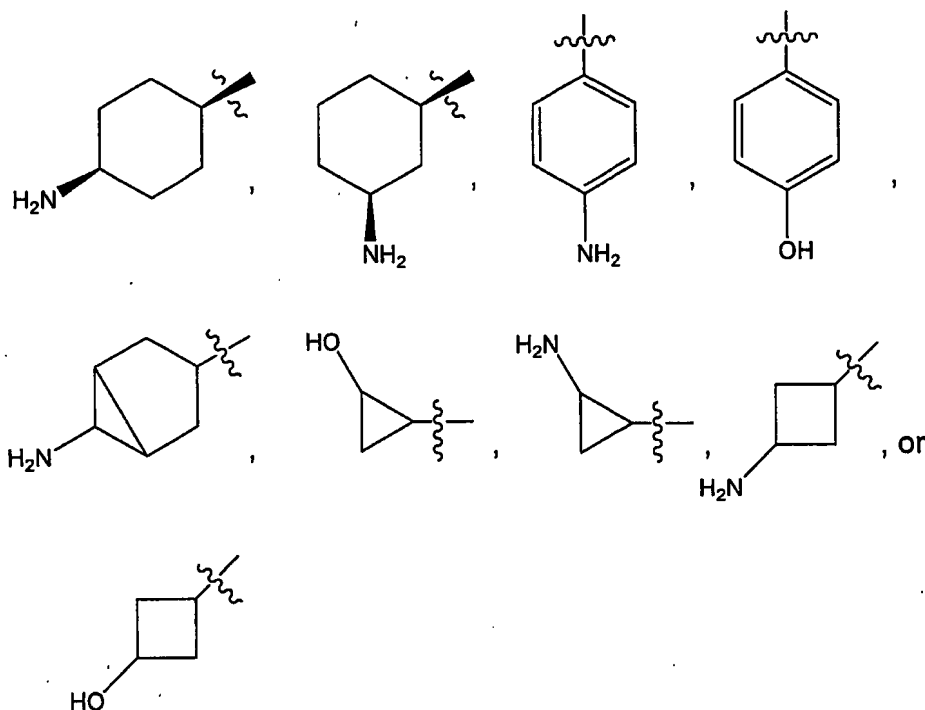
1 39. The compound of claim 38, wherein R^3 is selected from
2 substituted or unsubstituted pyridinyl, piperidinyl, piperazinyl, morpholinyl,
3 thiomorpholinyl, tetrahydrofuranyl, furanyl, pyrrolidinyl, pyrrolyl, thiophenyl,
4 tetrahydrothiophenyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl,
5 pyrazinyl, thiazolyl, pyrimidinyl, quinuclidinyl, indolyl, imidazolyl, triazolyl,
6 tetrazolyl, or pyridazinyl groups.

- 1 40. The compound of claim 29, wherein R^3 is selected from
 2 heteroaryl or heterocyclyl groups of formula



which may be additionally substituted or may be unsubstituted.

- 1 41. The compound of claim 29, wherein R^3 is selected from
2 aryl or cycloalkyl groups of formula



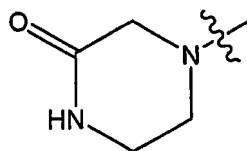
- 3 which may be additionally substituted or may be unsubstituted.
4

- 1 42. The compound of claim 29, wherein $R^{1'}$ and $R^{2'}$, together
2 with the nitrogen to which they are bound, form a substituted or unsubstituted
3 piperaziny group.

- 1 43. The compound of claim 42, wherein $R^{1'}$ and $R^{2'}$, together
2 with the nitrogen to which they are bound, form a piperaziny group that is
3 substituted with at least one group selected from, fluoromethyl,
4 difluoromethyl, or trifluoromethyl groups.

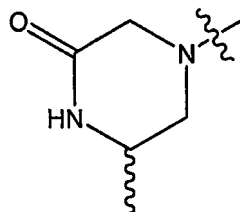
- 1 44. The compound of claim 42, wherein $R^{1'}$ and $R^{2'}$, together
2 with the nitrogen to which they are bound, form a piperaziny group
3 comprising at least one carbonyl group such that the piperaziny group is a
4 piperazinone that may be additionally substituted.

- 1 45. The compound of claim 44, wherein $R^{1'}$ and $R^{2'}$, together
2 with the nitrogen to which they are bound form a piperazinone of formula

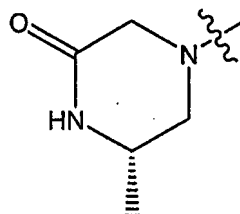


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4 which may be additionally substituted.

- 1 46. The compound of claim 45, wherein $R^{1'}$ and $R^{2'}$, together
2 with the nitrogen to which they are bound form a piperazinone of formula

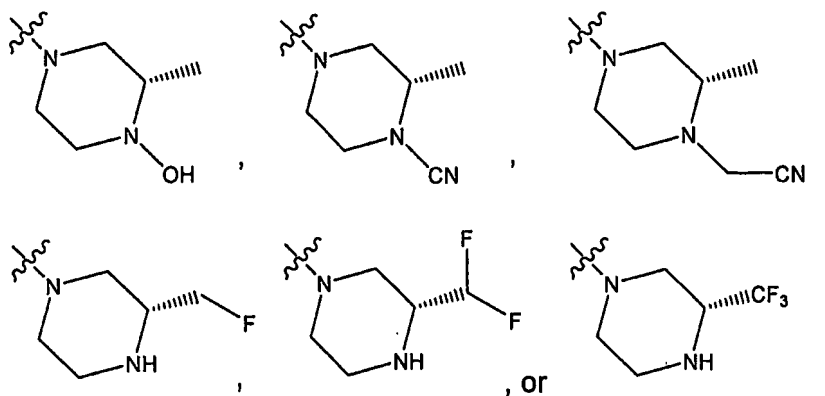


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1 47. The compound of claim 46, wherein $R^{1'}$ and $R^{2'}$, together
2 with the nitrogen to which they are bound form a piperazinone of formula

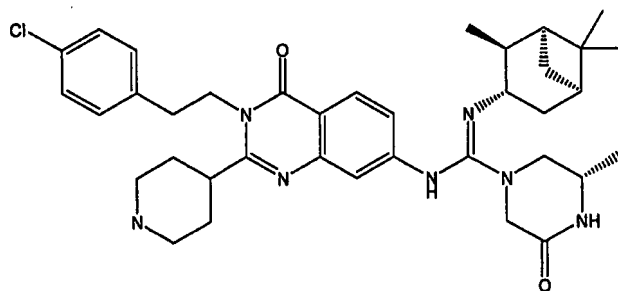


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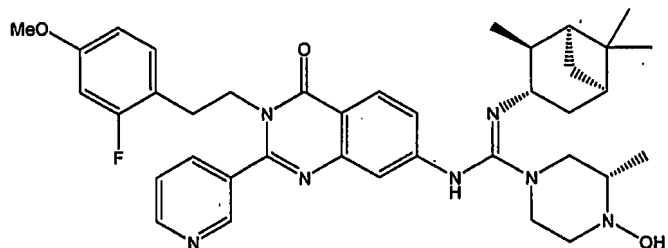
- 1 48. The compound of claim 42, wherein $R^{1'}$ and $R^{2'}$, together
2 with the nitrogen to which they are bound, form a piperazinyl group of formula



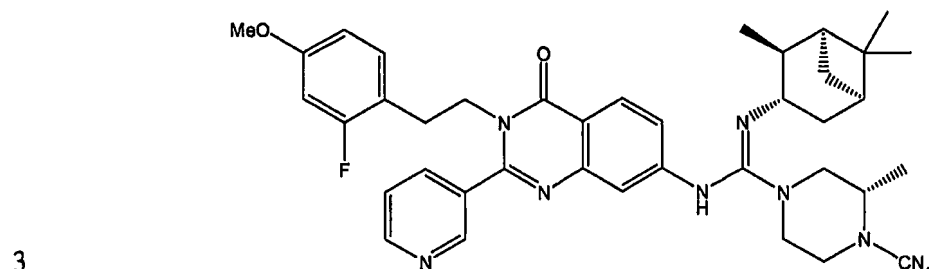
- 1 49. The compound of claim 29, wherein the compound is a
2 compound of formula



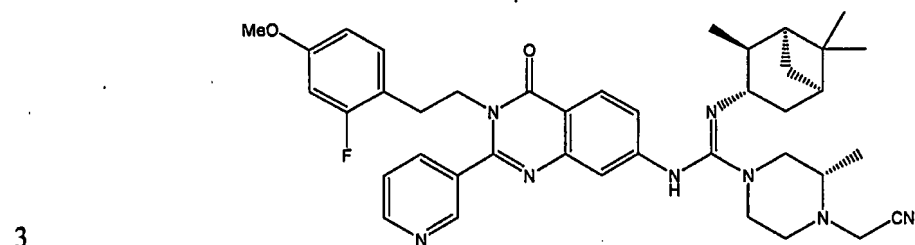
- 1 50. The compound of claim 29, wherein the compound is a
2 compound of formula



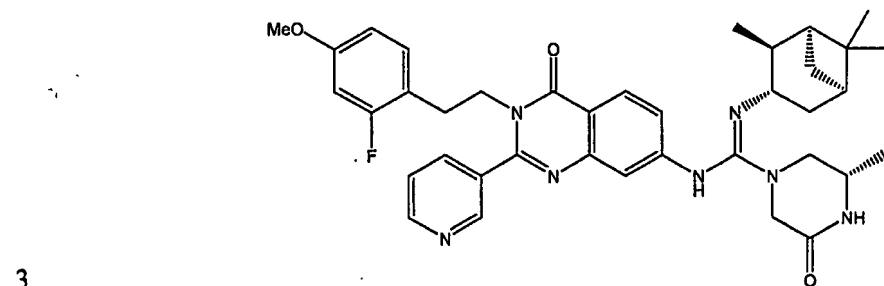
- 1 51. The compound of claim 29, wherein the compound is a
2 compound of formula



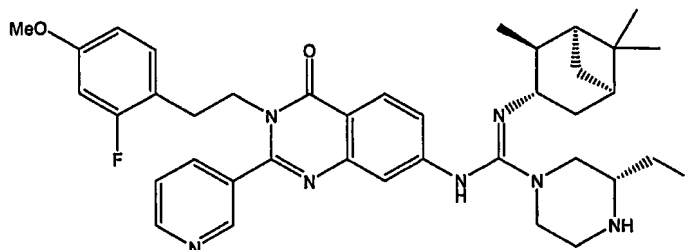
- 1 52. The compound of claim 29, wherein the compound is a
2 compound of formula



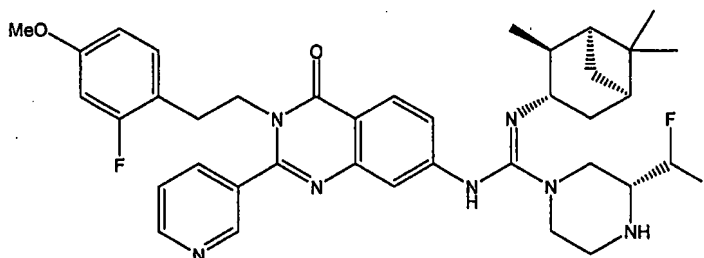
- 1 53. The compound of claim 29, wherein the compound is a
2 compound of formula



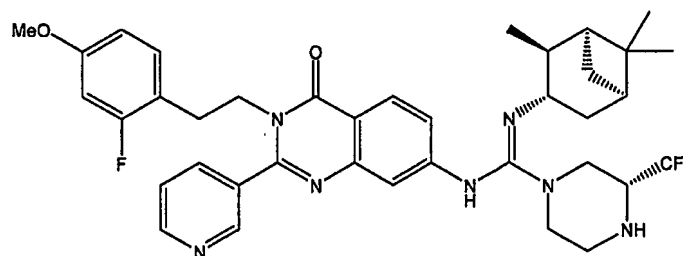
- 1 54. The compound of claim 29, wherein the compound is a
2 compound of formula



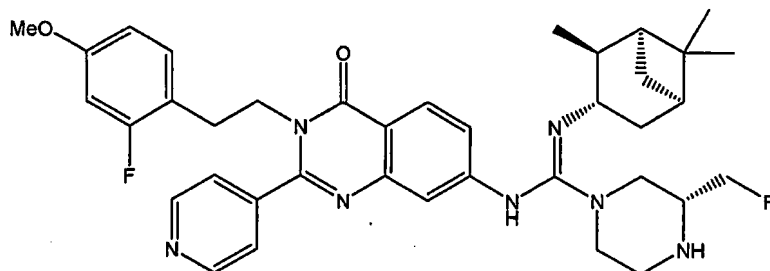
- 1 55. The compound of claim 29, wherein the compound is a
2 compound of formula



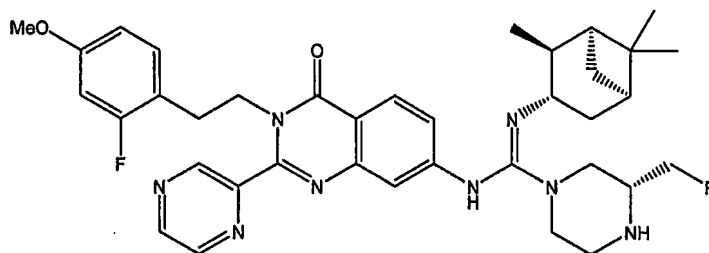
- 1 56. The compound of claim 29, wherein the compound is a
2 compound of formula



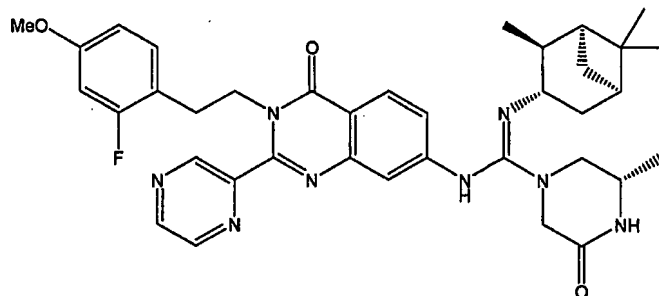
- 1 57. The compound of claim 29, wherein the compound is a
2 compound of formula



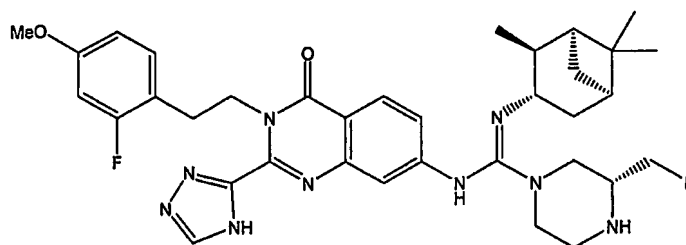
- 1 58. The compound of claim 29, wherein the compound is a
2 compound of formula



- 1 59. The compound of claim 29, wherein the compound is a
2 compound of formula

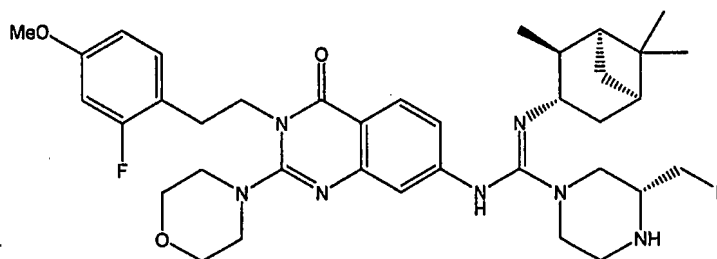


- 1 60. The compound of claim 29, wherein the compound is a
2 compound of formula



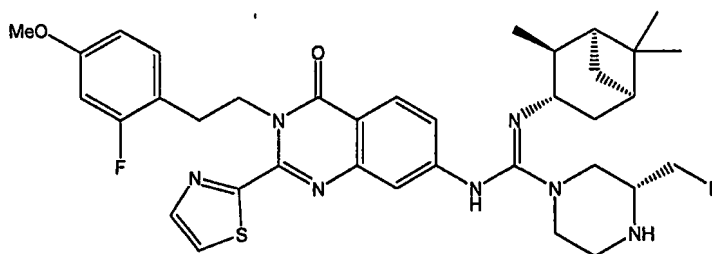
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- 1 61. The compound of claim 29, wherein the compound is a
2 compound of formula



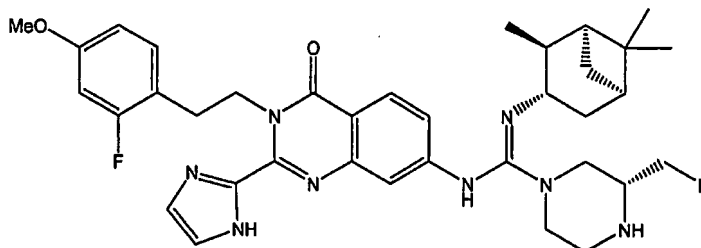
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- 1 62. The compound of claim 29, wherein the compound is a
2 compound of formula

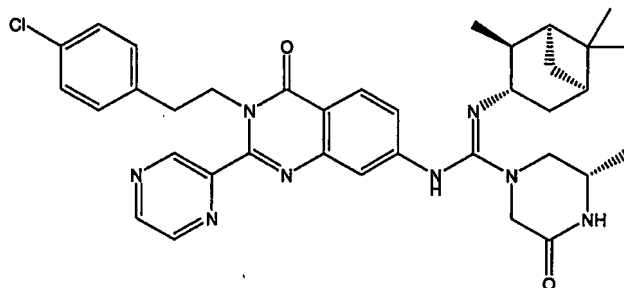


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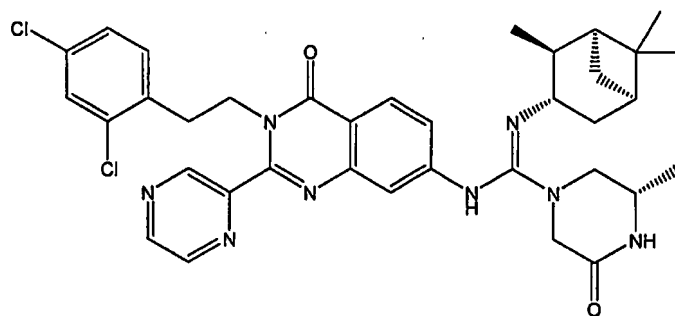
- 1 63. The compound of claim 29, wherein the compound is a
2 compound of formula



- 1 64. The compound of claim 29, wherein the compound is a
2 compound of formula



- 1 65. The compound of claim 29, wherein the compound is a
2 compound of formula



- 1 66. A pharmaceutical formulation comprising the compound
2 of any one of claims 29-65 and a pharmaceutically acceptable carrier.

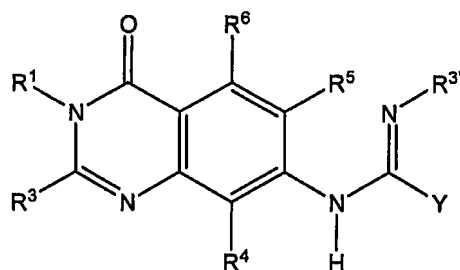
- 1 67. A method of treating an MC4-R mediated disease,
2 comprising administering to a subject in need thereof, the compound of any
3 one of claims 29-65.

1 68. The method according to claim 67, wherein the disease is
2 obesity or type II diabetes.

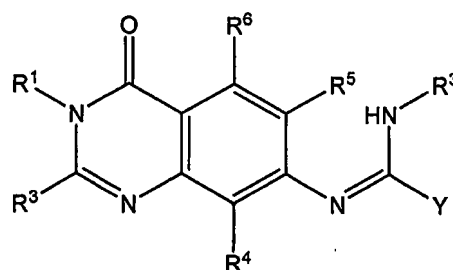
1 69. The method according to claim 67, wherein the
2 compound exhibits a $t_{1/2}$ value of less than 35 hours in a tissue with high
3 blood perfusion.

1 70. The method according to claim 69, wherein the tissue
2 with high blood perfusion is selected from a brain, a liver, a kidney or a heart.

1 71. A compound of formula VIIA, VIIB, mixtures thereof, or
2 pharmaceutically acceptable salts of the compound,



VIIA



VIIB

3
4 wherein

5 R^1 is selected from substituted or unsubstituted arylalkyl,
6 heteroarylalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, heterocyclalkyl,
7 cycloalkylalkyl, alkenyl, alkynyl, or alkyl groups;

8 R^3 is selected from H or substituted or unsubstituted arylalkyl,
9 heteroarylalkyl, alkoxy, alkylamino, dialkylamino, aryl, heteroaryl, heterocyclyl,
10 cycloalkyl, aminocycloalkyl, heterocyclalkyl, cycloalkylalkyl, alkenyl, alkynyl,
11 or alkyl groups;

12 R^4 , R^5 , and R^6 are independently selected from H, Cl, I, F, Br,
13 OH, NH₂, CN, NO₂, or substituted or unsubstituted alkoxy or alkyl groups;

1 $R^{2'}$, $R^{4'}$, and $R^{5'}$ are independently selected from H or
2 substituted or unsubstituted alkyl groups;

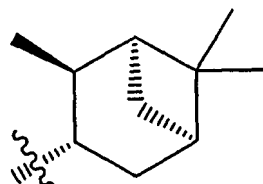
3 $R^{6'}$ is selected from substituted or unsubstituted alkyl groups; or
4 $R^{5'}$ and $R^{6'}$, together with the nitrogen to which they are bound, form a
5 heterocyclyl or heteroaryl group; and

6 $R^{7'}$ is selected from CN, or substituted or unsubstituted alkyl,
7 aryl, or arylalkyl groups.

1 72. The compound of claim 71, wherein R^4 , R^5 , and R^6 are all
2 H.

1 73. The compound of claim 71, wherein $R^{3'}$ is a substituted
2 or unsubstituted polycyclic cycloalkyl group.

1 74. The compound of claim 73, wherein $R^{3'}$ is a substituted
2 or unsubstituted polycyclic cycloalkyl group of formula VIII



VIII

1 75. The compound of claim 71, wherein R^1 is a substituted or
2 unsubstituted arylalkyl group.

1 76. The compound of claim 75, wherein R^1 is a substituted
2 phenylethyl group.

1 77. The compound of claim 76, wherein R^1 is a 4-substituted
2 phenylethyl group or is a 2,4-disubstituted phenylethyl group.

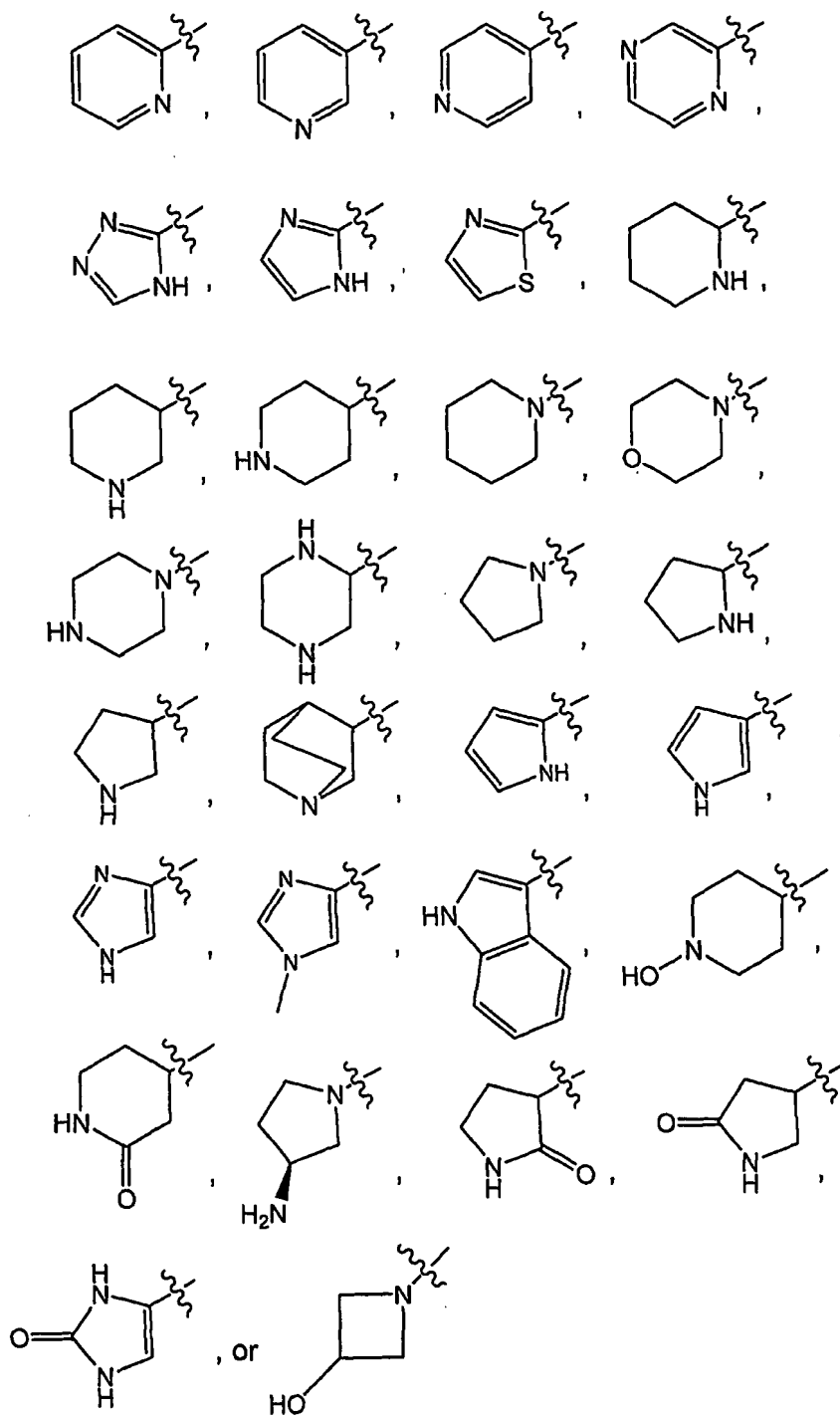
1 78. The compound of claim 75, wherein R^1 is selected from
2 2-fluoro-4-methoxyphenylethyl, 2-chloro-4-methoxyphenylethyl, 4-
3 fluorophenylethyl, 4-chlorophenylethyl, 4-chloro-2-fluorophenylethyl, 2,4-
4 dichlorophenylethyl, 4-bromophenylethyl, or 4-bromo-2-fluorophenylethyl
5 groups.

1 79. The compound of claim 78, wherein R^3 is selected from
2 substituted or unsubstituted heterocyclyl groups or substituted or
3 unsubstituted heteroaryl groups.

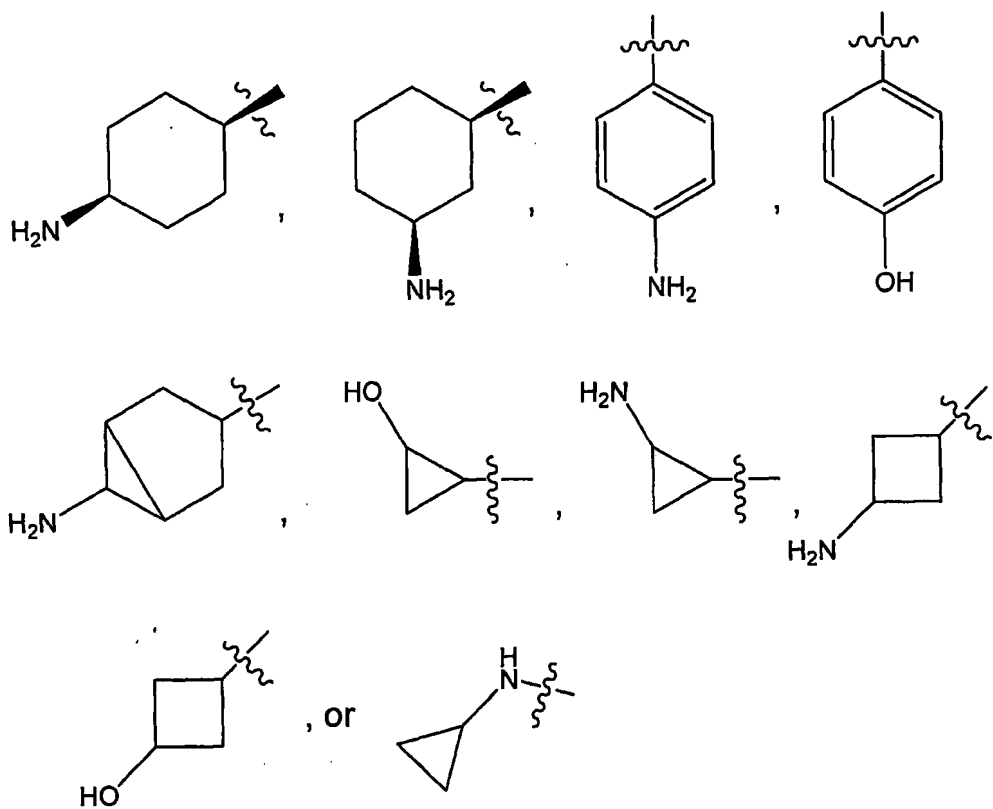
1 80. The compound of claim 79, wherein R^3 is selected from
2 substituted or unsubstituted pyridinyl, piperidinyl, piperazinyl, morpholinyl,
3 thiomorpholinyl, tetrahydrofuranyl, furanyl, pyrrolidinyl, pyrrolyl, thiophenyl,
4 tetrahydrothiophenyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl,
5 pyrazinyl, thiazolyl, pyrimidinyl, quinuclidinyl, indolyl, imidazolyl, triazolyl,
6 tetrazolyl, or pyridazinyl groups.

1 81. The compound of claim 71, wherein R^1 is selected from
2 phenylethyl, 2,4-dichlorophenylethyl, 4-methoxyphenylethyl, 4-
3 phenoxyphenylethyl, 4-bromophenylethyl, 4-methylphenylethyl, 4-
4 chlorophenylethyl, 4-fluorophenylethyl, 4-ethylphenylethyl, cyclohexenylethyl,
5 2-methoxyphenylethyl, 2-chlorophenylethyl, 2-fluorophenylethyl, 3-
6 methoxyphenylethyl, 3-fluorophenylethyl, thienylethyl, indolyethyl, 4-
7 hydroxyphenylethyl, 3,4-dimethoxyphenylethyl, 2-chloro-4-iodophenylethyl, 2-
8 fluoro-4-methylphenylethyl, 4-chloro-2-fluorophenylethyl, 4-bromo-2-
9 fluorophenylethyl, 2-fluoro-4-methoxyphenylethyl, 2-trifluoromethyl-4-
10 fluorophenylethyl, 2,4-difluorophenylethyl, 2,4-dimethylphenylethyl, 2,4-
11 dimethoxyphenylethyl, (2-pyridyl)ethyl, (3-pyridyl)ethyl, (4-pyridyl)ethyl,
12 (pyridyl)(hydroxymethyl)ethyl, or (phenyl)(hydroxymethyl)ethyl groups.

- 1 82. The compound of claim 71, wherein R^3 is selected from
 2 heteroaryl or heterocyclyl groups of formula



- 1 83. The compound of claim 71, wherein R^3 is selected from
2 aryl, cycloalkyl, or aminocycloalkyl groups of formula

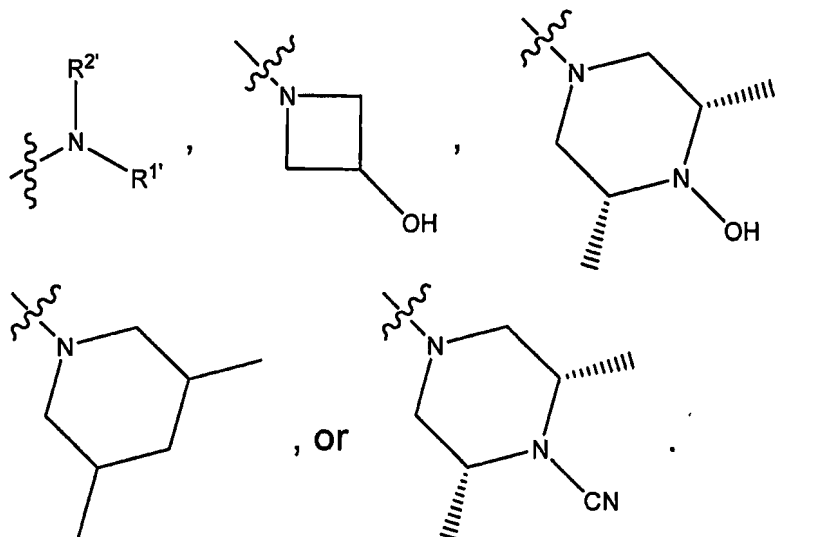


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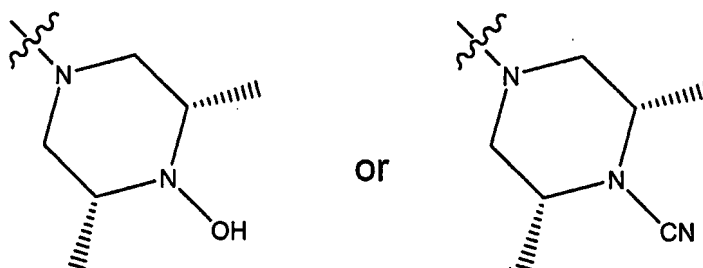
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which may be additionally substituted or may be unsubstituted.

1 84. The compound of claim 71, wherein Y is selected from



2
1 85. The compound of claim 84, wherein Y is selected from



1 86. A pharmaceutical formulation comprising a
2 pharmaceutically acceptable carrier and the compound of any one of claims
3 71-85.

1 87. A method of treating an MC4-R mediated disease,
2 comprising administering to a subject in need thereof, the compound of any
3 one of claims 71-85.

1 88. The method according to claim 87, wherein the disease is
2 obesity or type II diabetes.

- 1 89. The method according to claim 88, wherein the
2 compound exhibits a $t_{1/2}$ value of less than 35 hours in a tissue with high
3 blood perfusion.
- 1 90. The method according to claim 89, wherein the tissue
2 with high blood perfusion is selected from a brain, a liver, a kidney or a heart.
- 1 91. Use of a compound of any one of claims 29-66 or 71-85
2 in the preparation of a medicament for treating an MC4-R mediated disease.
- 1 92. The use of claim 91, wherein the MC4-R mediated
2 disease is obesity or type II diabetes.